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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,856	09/11/2003	Eszter Birck-Wilson	G0744.70028US01	5220

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

MAIL DATE	DELIVERY MODE
07/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,856	BIRCK-WILSON ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,31-44,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,31-44,57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The amendment filed 07 May 2007 is acknowledged and has been entered. Claims 22-30, 45-56, 58, and 62 have been cancelled. Claims 1-21, 31-44, 57, and 59-61 remain in the case. Claims 57 and 59-61 have been withdrawn from further consideration as being drawn to a non-elected species, there being no allowable generic or linking claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 1-21, 31-44, 57, and 59-61 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons of record as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims. As set forth, one would not readily envision any starting samples for use other than those containing IgG4 absent further guidance and unpredictable experimentation. As also set forth, unguided, random, unpredictable experimentation to determine functional conditions for IgG4 half and whole antibody separation other than those taught in the specification is undue.

Applicant's arguments filed 07 May 2007 have been fully considered but they are not deemed to be persuasive.

Applicant urges that the listing of antibodies other than IgG4 is sufficient to enable the invention as claimed. This is not found persuasive for the reasons of record, particularly because immunoglobulin isotypes other than IgG4 are not known to predictably produce mixtures of half and whole antibodies amenable to use in the instant method. The teachings of Angal et al. (e.g., "IgG4 differs from the other human IgG isotypes . . .") noted by the examiner are also supported by the teachings of King et al. (e.g., see page 320, col. 2) and by the instant "Abstract of the Disclosure." Applicant also urges that the use of hydrophobic columns is within the skill of one in the art. This is not found persuasive for the reasons of record. With regard to both arguments above, as the court stated in the decision of *Genentech Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (CAFC 1997), "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 10, 12-15, 20, and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by King et al. (Biochem. J. 281: 317, 1992) in light of Colcher et al. (Cancer Res. 49: 1738, 1989) and either of Schuurman et al. (Molecular Immunol. 38: 1, 2001) or the instant disclosure. In addition to the teachings of the reference noted in the previous Office action, the reference teaches that the Protein A-Sepharose and ion exchange chromatography method of Colcher et al. was used for purification of the IgG4 mixtures. This method involved lowering of the pH with a linear pH gradient to levels capable of dissociating non-covalently bound immunoglobulins, in light of Schuurman et al. (see page 6) or the instant disclosure.

Applicant's arguments filed 07 May 2007 have been fully considered but they are not deemed to be persuasive. Applicant's arguments regarding the teaching of reduction of pH in the reference were not found persuasive for the reasons of record and those as set forth above. Notwithstanding applicant's assertions to the contrary, recitations of intended use, or of an intended result, or of a characterization of the results of the active step(s) do not result in a manipulative difference as compared to the prior art and, therefore, are accorded no patentable weight.

Claims 1, 2, 5, 8, 9, 12, and 20 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Palmer et al. (Biochem. 3: 863, 1964).

Palmer et al. reduced rabbit IgG prepared from serum samples to produce a proportion of half-IgG molecules in the preparations, the pH was reduced to dissociate the non-covalent interactions of the half-IgG molecules, and the reduced and lowered pH sample was applied to a column to separate the half-IgG and whole IgG molecules (see e.g. Fig. 3).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-5, 8-21, and 31-42 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over the combined teachings of King et al. (Biochem. J. 281: 317, 1992), Schuurman et al. (Molecular Immunol. 38: 1, 2001), Angal et al. (Mol. Immunol. 30: 105, 1993), and Palmer et al. (Biochem. 3: 863, 1964).

King et al. teach mixtures containing IgG4 half (including preparations of Fab') and whole (including $F(ab')_2$) chimeric or myeloma antibodies and applied the mixtures to series of columns including ion exchange columns. The reference teaches the desirability of separating the half from the whole antibodies for further studies of the hinge region of the molecules (see e.g. pages 321-322), but did not separate the molecules other than by sodium dodecyl sulfate polyacrylamide gel electrophoresis, including with a rod (i.e. columnar) gel.

Schuurman et al. teach the equilibrium of half and whole human IgG4 antibodies and also teach IgG4 hinge mutants with reduced ability to form half antibody molecules. The reference suggests that the non-covalent interactions of half antibodies, particularly the interactions

between the C_H3 domains, can be dissociated by denaturing conditions such as low pH (see e.g. page 6).

Palmer et al. teach dissociation of the non-covalent interactions of half-IgG molecules by low pH and size exclusion chromatography for the separation of dissociated half from whole IgG.

Angal et al. teach the chimeric antibody of King et al. having a further mutation in the hinge region to a sequence similar to that found in IgG1 and IgG2, a mutation which essentially abolishes the half IgG4 antibody molecules in the preparations. The reference suggests partial resolution of the non-mutated half and whole antibodies by ion exchange chromatography, but does not provide details therefor (see page 105).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have separated half and whole antibodies, particularly human or chimeric IgG4 as suggested in King et al., with a reasonable expectation of success by reducing the pH of a sample prior to a column separation, because a reduction in pH is directly suggested by Schuurman et al. or Palmer et al. for the dissociation of non-covalently associated antibodies, specifically prior to a column separation (Palmer et al.). One would have reasonably expected either of size exclusion (Palmer et al.) or ion exchange (Angal et al.) chromatography to have performed the separation because these were known to the art to function for the separation of dissociated half from whole antibodies. One would have reasonably expected that the source of the antibody would not have affected the presence of a mixture because the ability to form half antibodies is a property of some antibody isotypes (King et al., Schuurman et al., Angal et al.) or

of some treatments (Palmer et al.) and one would have reasonably expected that the source of the antibody mixture would not have affected the downstream separation.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JLG

James L. Grun, Ph.D.
July 2, 2007

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